


ATTACHMENT 2

CEBERT PHARMACEUTICALS, INC.

DISKETTS® 
 Dispersible Tablets
 (Methadone Hydrochloride
 Tablets USP), 40 mg
 For Methadone Treatment Programs

Rx only

CONDITIONS FOR DISTRIBUTION AND
 USE OF METHADONE PRODUCTS:
 Code of Federal Regulations,
 Title 21, Sec. 291.505

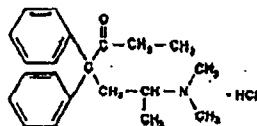
METHADONE PRODUCTS, WHEN USED FOR THE TREATMENT OF NARCOTIC ADDICTION IN DETOXIFICATION OR MAINTENANCE PROGRAMS, SHALL BE DISPENSED ONLY BY APPROVED HOSPITAL PHARMACIES, APPROVED COMMUNITY PHARMACIES, AND MAINTENANCE PROGRAMS APPROVED BY THE FOOD AND DRUG ADMINISTRATION AND THE DESIGNATED STATE AUTHORITY.

APPROVED MAINTENANCE PROGRAMS SHALL DISPENSE AND USE METHADONE IN ORAL FORM ONLY AND ACCORDING TO THE TREATMENT REQUIREMENTS STIPULATED IN THE FEDERAL METHADONE REGULATIONS (21 CFR 291.505).

FAILURE TO ABIDE BY THE REQUIREMENTS IN THESE REGULATIONS MAY RESULT IN CRIMINAL PROSECUTION, SEIZURE OF THE DRUG SUPPLY, REVOCATION OF THE PROGRAM APPROVAL, AND INJUNCTION PRECLUDING OPERATION OF THE PROGRAM.

DESCRIPTION

Methadone Hydrochloride, USP, (3-heptanone, 6-(dimethylamino)-4,4-diphenyl-hydrochloride), is a white, essentially odorless, bitter-tasting, crystalline powder. It is very soluble in water, soluble in isopropanol and in chloroform, and practically insoluble in ether and in glycerine. Methadone hydrochloride has a pKa of 8.25 in water at 20°C. Its molecular weight is 345.91 and it has the following structural formula.



The Disket® preparation of methadone hydrochloride has been specially formulated with insoluble excipients to deter the use of this drug by injection. Methadone hydrochloride has the empirical formula $C_{21}H_{27}NO \cdot HCl$, and its molecular weight is 345.91.

Each Disket contains 40 mg (0.116 mmol) methadone hydrochloride. Each tablet also contains microcrystalline cellulose, pregelatinized starch, potassium phosphate monobasic, colloidal silicon dioxide, stearic acid, magnesium stearate, orange lake color and orange-pineapple flavor.

ACTIONS

Methadone hydrochloride is a synthetic narcotic analgesic with multiple actions quantitatively similar to those of morphine, the most prominent of which involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value are analgesia and sedation and detoxification or maintenance in narcotic addiction. The methadone abstinence syndrome, although qualitatively similar to that of morphine, differs in that the onset is slower, the course is more prolonged, and the symptoms are less severe.

When administered orally, methadone is approximately one-half as potent as when given parenterally. Oral administration results in a delay of the onset, a lowering of the peak, and an increase in the duration of analgesic effect.

INDICATIONS

1. Detoxification treatment of narcotic addiction (heroin or other morphine-like drugs).
2. Maintenance treatment of narcotic addiction (heroin or other morphine-like drugs), in conjunction with appropriate social and medical services.

NOTE

If methadone is administered for treatment of heroin dependence for more than three weeks, the procedure passes from treatment of the acute withdrawal syndrome (detoxification) to maintenance therapy. Maintenance treatment is permitted to be undertaken only by approved methadone programs. This does not preclude the maintenance treatment of an addict who is hospitalized for medical conditions other than addiction and who requires temporary maintenance during this critical period of his/her stay or whose enrollment has been verified in a program which has approval for maintenance treatment with methadone.

CONTRAINDICATIONS

Hypersensitivity to methadone.

WARNINGS

Diskets Methadone Hydrochloride are for oral administration only. This preparation contains insoluble excipients and therefore *must not* be injected. It is required that Diskets Methadone Hydrochloride, if dispensed, be packaged in child-resistant containers and kept out of the reach of children to prevent accidental ingestion.

Methadone hydrochloride, a narcotic, is a Schedule II controlled substance under the Federal Controlled Substances Act. Appropriate security measures should be taken to safeguard stocks of methadone against diversion.

DRUG DEPENDENCE - METHADONE CAN PRODUCE DRUG DEPENDENCE OF THE MORPHINE TYPE AND, THEREFORE, HAS THE POTENTIAL FOR BEING ABUSED. PSYCHIC DEPENDENCE, PHYSICAL DEPENDENCE, AND TOLERANCE MAY DEVELOP ON REPEATED ADMINISTRATION OF METHADONE, AND IT SHOULD BE PRESCRIBED AND ADMINISTERED WITH THE SAME DEGREE OF CAUTION APPROPRIATE TO THE USE OF MORPHINE.

Interaction with Other Central Nervous System Depressants - Methadone should be used with caution and in reduced dosage in patients who are concurrently receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, tricyclic antidepressants, and other CNS depressants (including alcohol). Respiratory depression, hypotension, and profound sedation or coma may result.

Anxiety - Since methadone, as used by tolerant subjects at a constant maintenance dosage, is not a tranquilizer, patients who are maintained on this drug will react to life problems and stresses with the same symptoms of anxiety as do other individuals. The physician should not confuse such symptoms with those of narcotic abstinence and should not attempt to treat anxiety by increasing the dosage of methadone. The action of methadone in maintenance treatment is limited to the control of narcotic symptoms and is ineffective for relief of general anxiety.

Head Injury and Increased Intracranial Pressure - The respiratory depressant effects of methadone and its capacity to elevate cerebrospinal-fluid pressure may be markedly exaggerated in the presence of increased intracranial pressure. Furthermore, narcotics produce side effects that may obscure the clinical course of patients with head injuries. In such patients, methadone must be used with caution and only if it is deemed essential.

Asthma and Other Respiratory Conditions - Methadone should be used with caution in patients having an acute asthmatic attack, in those with chronic obstructive pulmonary disease or cor pulmonale, and in individuals with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia, or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Hypotensive Effect - The administration of methadone may result in severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume or concurrent administration of such drugs as the phenothiazines or certain anesthetics.

Use in Ambulatory Patients - Methadone may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery. The patient should be cautioned accordingly.

Methadone, like other narcotics, may produce orthostatic hypotension in ambulatory patients.

Use in Pregnancy - Safe use in pregnancy has not been established in relation to possible adverse effects on fetal development. Therefore, methadone should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS

Drug Interactions:

Pentazocine - Patients who are addicted to heroin or who are on the methadone maintenance program may experience withdrawal symptoms when given an opioid agonist-antagonist, such as pentazocine.

Rifampin - The concurrent administration of rifampin may possibly reduce the blood concentration of methadone to a degree sufficient to produce withdrawal symptoms. The mechanism by which rifampin may decrease blood concentrations of methadone is not fully understood, although enhanced microsomal drug-metabolized enzymes may influence drug disposition.

Monoamine Oxidase (MAO) Inhibitors - Therapeutic doses of meperidine have precipitated severe reactions in patients concurrently receiving monoamine oxidase inhibitors or those who have received such agents within 14 days. Similar reactions thus far have not been reported with methadone; but if the use of methadone is necessary in such patients, a sensitivity test should be performed in which repeated small incremental doses are administered over the course of several hours while the patient's condition and vital signs are under careful observation.

Desipramine - Blood levels of desipramine have increased with concurrent methadone therapy.

Special-Risk Patients - Methadone should be given with caution and the initial dose should be reduced in certain patients, such as the elderly or debilitated and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease, prostatic hypertrophy, or urethral stricture.

Acute Abdominal Conditions - The administration of methadone or other narcotics may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

ADVERSE REACTIONS

Heroin Withdrawal - During the induction phase of methadone maintenance treatment, patients are being withdrawn from heroin and may therefore show typical withdrawal symptoms, which should be differentiated from methadone-induced side effects. They may exhibit some or all of the following symptoms associated with acute withdrawal from heroin or other opiates: lacrimation, rhinorrhea, sneezing, yawning, excessive perspiration, goose-flesh, fever, chilliness alternating with flushing, restlessness, irritability, "sleepy yawn", weakness, anxiety, depression, dilated pupils, tremors, tachycardia, abdominal cramps, body aches, involuntary twitching and kicking movements, anorexia, nausea, vomiting, diarrhea, intestinal spasms, and weight loss.

Initial Administration - Initially, the dosage of methadone should be carefully titrated to the individual. Induction too rapid for the patient's sensitivity is more likely to produce the following effects.

THE MAJOR HAZARDS OF METHADONE, AS OF OTHER NARCOTIC ANALGESICS, ARE RESPIRATORY DEPRESSION AND, TO A LESSER DEGREE, CIRCULATORY DEPRESSION. RESPIRATORY ARREST, SHOCK, AND CARDIAC ARREST HAVE OCCURRED.

The most frequently observed adverse reactions include lightheadedness, dizziness, sedation, nausea, vomiting, and sweating. These effects seem to be more prominent in ambulatory patients and in those who are not suffering severe chronic pain. In such individuals, lower doses are advisable. Some adverse reactions may be alleviated in the ambulatory patient if he lies down.

Other adverse reactions include the following:

Central Nervous System - Euphoria, dysphoria, weakness, headache, insomnia, agitation, disorientation, and visual disturbances.

Gastrointestinal - Dry mouth, anorexia, constipation and biliary tract spasm.

Cardiovascular - Flushing of the face, bradycardia, palpitation, faintness, and syncope.

Genitourinary - Urinary retention or hesitancy, antidiuretic effect, and reduced libido and/or potency.

Allergic - Pruritus, urticaria, other skin rashes, edema, and, rarely, hemorrhagic urticaria.

Hematologic - Reversible thrombocytopenia has been described in a narcotics addict with chronic hepatitis.

Maintenance on a Stabilized Dose - During prolonged administration of methadone, as in a methadone maintenance treatment program, there is a gradual, yet progressive, disappearance of side effects over a period of several weeks. However, constipation and sweating often persist.

OVERDOSAGE

Signs and Symptoms - Methadone is an opioid and produces effects similar to those of morphine. Symptoms of overdose begin within seconds after intravenous administration and within minutes of nasal, oral, or rectal administration. Prominent symptoms are miosis, respiratory depression, somnolence, coma, cool clammy skin, skeletal muscle flaccidity that may progress to hypotension, apnea, bradycardia, and death. Noncardiac pulmonary

edema may occur, and monitoring of heart filling pressures may be helpful.

Treatment - To obtain up-to-date information about the treatment of overdose, a good resource is your certified Regional Poison Control Center. Telephone numbers of certified poison control centers are listed in the *Physicians' Desk Reference (PDR)*. In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and usual drug kinetics in your patient.

Initial management of opioid overdose should include establishment of a secure airway and support of ventilation and perfusion. Naloxone may be given to antagonize opioid effects, but the airway must be secured as vomiting may ensue. The duration of methadone effect is much longer (36 to 48 hours) than the duration of naloxone effect (1 to 3 hours), and repeated doses (or continuous intravenous infusion) of naloxone may be required.

If the patient has chronically abused opioids, administration of naloxone may precipitate a withdrawal syndrome that may include yawning, tearing, restlessness, sweating, dilated pupils, piloerection, vomiting, diarrhea, and abdominal cramps. If these symptoms develop, they should abate quickly as the effects of naloxone dissipate.

If methadone has been taken by mouth, protect the patient's airway and support ventilation and perfusion. Meticulously monitor and maintain, within acceptable limits, the patient's vital signs, blood gases, serum electrolytes, etc. Absorption of drugs from the gastrointestinal tract may be decreased by giving activated charcoal, which, in many cases, is more effective than emesis or lavage; consider charcoal instead of or in addition to gastric emptying. Repeated doses of charcoal over time may hasten elimination of some drugs that have been absorbed. Safeguard the patient's airway when employing gastric emptying or charcoal.

Forced diuresis, peritoneal dialysis, hemodialysis, or charcoal hemoperfusion have not been established as beneficial for an overdose of methadone.

NOTE

IN AN INDIVIDUAL PHYSICALLY DEPENDENT ON NARCOTICS, THE ADMINISTRATION OF THE USUAL DOSE OF A NARCOTIC ANTAGONIST WILL PRECIPITATE AN ACUTE WITHDRAWAL SYNDROME. THE SEVERITY OF THIS SYNDROME WILL DEPEND ON THE DEGREE OF PHYSICAL DEPENDENCE AND THE DOSE OF THE ANTAGONIST ADMINISTERED. THE USE OF A NARCOTIC ANTAGONIST IN SUCH A PERSON SHOULD BE AVOIDED IF POSSIBLE. IF IT MUST BE USED TO TREAT SERIOUS RESPIRATORY DEPRESSION IN THE PHYSICALLY DEPENDENT PATIENT, THE ANTAGONIST SHOULD BE ADMINISTERED WITH EXTREME CARE AND BY TITRATION WITH SMALLER THAN USUAL DOSES OF THE ANTAGONIST.

DOSAGE AND ADMINISTRATION

For Detoxification Treatment - THE DRUG SHALL BE ADMINISTERED DAILY UNDER CLOSE SUPERVISION AS FOLLOWS:

A detoxification treatment course shall not exceed 21 days and may not be repeated earlier than 4 weeks after completion of the preceding course.

In detoxification, the patient may receive methadone when there are significant symptoms of withdrawal. The dosage schedules indicated below are recommended but could be varied in accordance with clinical judgment. Initially, a single oral dose of 15 to 20 mg of methadone will often be sufficient to suppress withdrawal symptoms. Additional methadone may be provided if withdrawal symptoms are not suppressed or if symptoms reappear. When patients are physically dependent on high doses, it may be necessary to exceed these levels. Forty mg/day in single or divided doses will usually constitute an adequate stabilizing dosage level. Stabilization can be continued for 2 to 3 days, and then the amount of methadone normally will be gradually decreased. The rate at which methadone is decreased will be determined separately for each patient. The dose of methadone can be decreased on a daily basis or at 2-day intervals, but the amount of intake shall always be sufficient to keep withdrawal symptoms at a tolerable level. In hospitalized patients, a daily reduction of 20% of the total daily dose may be tolerated and may cause little discomfort. In ambulatory patients, a somewhat slower schedule may be needed. If methadone is administered for more than 3 weeks, the procedure is considered to have progressed from detoxification or treatment of the acute withdrawal syndrome to maintenance treatment, even though the goal and intent may be eventual total withdrawal.

For Maintenance Treatment - In maintenance treatment, the initial dosage of methadone should control the abstinence symptoms that follow withdrawal of narcotic drugs but should not be so great as to cause sedation, respiratory depression, or other effects of acute intoxication. It is important that the initial dosage be adjusted on an individual basis to the narcotic tolerance of the new patient. If such a patient has been a heavy user of heroin up to the day of admission, he/she may be given 20 mg 4 to 8 hours later or 40 mg in a single oral dose. If the patient enters treatment with little or no narcotic tolerance (e.g., if he/she has recently been released from jail or other confinement), the initial dosage may be one half these quantities. When there is any doubt, the smaller dose should be used initially. The patient should then be kept under observation, and, if symptoms of abstinence are distressing, additional 10-mg doses may be administered as needed. Subsequently, the dosage should be adjusted individually, as tolerated and required, up to a level of 120 mg daily. The patient will initially ingest the drug under observation daily, or at least 8 days a week, for the first 3 months. After demonstrating satisfactory adherence to the program regulations for at least 3 months, the patient may be permitted to reduce to 3 times weekly the occasions when he/she must ingest the drug under observation. The patient shall receive no more than a 2-day take-home supply. With continuing adherence to the program's requirements for at least 2 years, he/she may then be permitted twice-weekly visits to the program for drug ingestion under observation, with a 3-day take-home supply. A daily dose of 120 mg or more shall be justified in the medical record. Prior approval from state authority and the Food and Drug Administration is required for any dose above 120 mg administered at the clinic and for any dose above 100 mg to be taken at home. A regular review of dosage level should be made by the responsible physician, with careful consideration given to reduction of dosage as indicated on an individual basis. A new dosage level is only a test level until stability is achieved.

Special Considerations for a Pregnant Patient - Caution shall be taken in the maintenance treatment of pregnant patients. Dosage levels shall be kept as low as possible if continued methadone treatment is deemed necessary. It is the responsibility of the program sponsor to assure that each female patient be fully informed concerning the possible risks to a pregnant woman or her unborn child from the use of methadone.

Special Limitations-

Treatment of Patients Under Age 18

1. The safety and effectiveness of methadone for use in the treatment of adolescents have not been proved by adequate clinical study. Special procedures are therefore necessary to assure that patients under age 16 will not be admitted to a program and that patients between 16 and 18 years of age will be admitted to maintenance treatment only under limited conditions.
2. Patients between 16 and 18 years of age who were enrolled and under treatment in approved programs on December 15, 1972, may continue in maintenance treatment. No new patients between 16 and 18 years of age may be admitted to a maintenance treatment program after March 15, 1973, unless a parent, legal guardian, or responsible adult designated by the state authority completes and signs Form FD 2635, "Consent for Methadone Treatment."

Methadone treatment of new patients between the ages of 16 and 18 years will be permitted after December 15, 1972, only with a documented history of 2 or more unsuccessful attempts at detoxification and a documented history of dependence on heroin or other morphine-like drugs beginning 2 years or more prior to application for treatment. No patient under age 16 may be continued or started on methadone treatment after December 15, 1972, but these patients may be detoxified and retained in the program in a drug-free state for follow-up and aftercare.

3. Patients under age 18 who are not placed on maintenance treatment may be detoxified. Detoxification may not exceed 3 weeks. A repeat episode of detoxification may not be initiated until 4 weeks after the completion of the previous detoxification.

HOW SUPPLIED

DISKETTS® Dispersible Tablets

Methadone Hydrochloride

Tablets USP, 40 mg

40 mg peach cross-scored tablets (Identified 54 883).

NDC 64019-538-25: Bottles of 100 tablets.

Store at 25°C (77°F); excursions permitted
to 15°-30°C (59°-86°F)

[see USP Controlled Room Temperature].

Mfd. by: Roxane Laboratories, Inc.

Columbus, Ohio 43216

Dist. by: Cebert Pharmaceuticals, Inc.

Birmingham, Alabama 35242

10000879/01

Revised April 2002

© RLI, 2002

